Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW

Adipose tissue dysfunction and MAFLD in obesity on the scene of COVID-19

Adryana Cordeiro[a,b,*], **Amanda Ribamar**[a,c], **Andrea Ramalho**[a]

[a] *Department of Social Applied Nutrition, Micronutrients Research Center (NPqM), Institute of Nutrition, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*
[b] *Department of Biomedicine, Unit of Biochemistry, Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal*
[c] *Faculty of Medicine, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil*

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Abstract Obesity is a known risk factor for respiratory infection and many other chronic diseases, including metabolic dysfunction-associated fatty liver disease (MAFLD), previously known as nonalcoholic fatty liver disease (NAFLD). Recently, it has been considered an important and independent predictor for coronavirus disease 2019 (COVID-19) complications in adults, especially cardiopulmonary, presenting in a great number of individuals in critical care. In obesity, adipose tissue (AT) undergoes expansion via several processes: expansion of adipocytes and insufficient vascularization lead to hypoxia; adipocyte apoptosis/necrosis; irregular fatty acid flux; and enhanced secretion of inflammatory adipokines, cytokines, and chemokines. In individuals with obesity the liver can also become a target of COVID-19 infection, although major liver damage is uncommon. COVID-19 acute pandemic often develops in patients with major metabolic abnormalities, including fatty liver disease, which is part of a chronic pandemic together with body fat accumulation. During metabolic abnormalities, the expansion of metabolically active fat parallels chronic inflammatory changes, the development of Insulin Resistance (IR), and in the liver, the accumulation of fat, possibly, an underlying fibrosis. SARS-Cov-2 virus might affect the liver by direct or indirect mechanisms.

The current epidemic of obesity and related metabolic diseases has extensively contributed to increase the number of severe cases and deaths from COVID-19, resulting in a health, political and economic crisis with long-lasting consequences.

In this review, the authors explore the relationship between AT dysfunction and MAFLD in obesity on the scene of COVID-19.

* Corresponding author.
E-mail address: contato@adryanacordeiro.com (A. Cordeiro).

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Introduction

Obesity is a known risk factor for respiratory infection and many other chronic diseases, including hypertension, dyslipidemia, metabolic dysfunction-associated fatty liver disease (MAFLD), previously known as nonalcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus (DM2), cardiovascular disease [1] and several types of cancer [2]. Additionally, has been considered an important and independent predictor for coronavirus disease 2019 (COVID-19) complications in adults, especially cardiopulmonary [3], presenting in a large number of individuals in critical care.

Obesity, *per si*, changes the composition, structure, and function of adipose tissue (AT). Responding to excessive calorie intake, AT undergoes expansion via two processes: hyperplasia (increase in adipocyte number) and hypertrophy (increase in adipocytes size). As a consequence of excessive or abnormal fat tissue accumulation, obesity can also alter innate and adaptive immune responses, making the immune system more prone to infections and less responsive to vaccinations, antivirals, and antimicrobial drugs [4].

The infection by SARS-CoV-2 virus represents a systemic disease [5], COVID-19, that causes a severe acute respiratory syndrome which can lead to heart failure, myocardial injury [6,7], myocarditis, vascular inflammation, cardiac arrhythmias [7], hypoxic encephalopathy [8], multi-organ failure, and lastly death [9]. The COVID-19 pandemic poses a devastating challenge to the global health system and the economy.

Angiotensin-converting enzyme 2 (ACE2) receptor expression also occur in vascular endothelium, in the brush border of intestinal enterocytes [10,11], and in cholangiocytes [10]. Thus, the symptomatic involvement of the gastrointestinal tract is possible with COVID-19 [12-15]. The presence of ACE2 receptors in the glandular cells of gastric, duodenal and distal enterocytes may result in malabsorption, unbalanced intestinal secretion and activation of the enteric nervous system, leading to gastrointestinal symptoms [16,17].

The liver can also become a target of COVID-19 infection, although major liver damage is uncommon [18-21]. SARS-Cov-2 might affect the liver by direct (i.e., viral translocation from the gut to the liver) or indirect mechanisms (i.e., systemic inflammation, effects on pre-existing liver diseases, liver ischemia and hypoxia and drug-related liver injury) [21].

Remarkably, MAFLD is a chronic dysmetabolic pandemic which has become the most common liver disease worldwide, with a high prevalence in the population with obesity [22,23]. MAFLD does not stands on its own, but it is usually associated with a several risk factors [24]. About this view, the acronym NAFLD has been recently re-visited for minting the acronym MAFLD [24]. MAFLD can therefore affect the final outcome in COVID-19 patients [25-28].

In this review, the authors explore the relationship between AT dysfunction and MAFLD in obesity on the scene of COVID-19.

Adipose tissue dysfunction and SARS-cov-2 in obesity

AT is a dynamic and crucial endocrine organ, secreting adipose tissue-derived hormones like adipokines/lipokines, endocrine factors, extracellular vesicles, enzymes, mRNAs and microRNAs (miRNAs) modulating energy balance, glucose and lipid homeostasis, tissue repair, homeostasis, inflammatory and immune response [29,30].

In Obesity, AT undergoes expansion via several processes: expansion of adipocytes and insufficient vascularization lead to hypoxia; adipocyte apoptosis/necrosis; irregular fatty acid flux; and enhanced secretion of inflammatory adipokines, cytokines, and chemokines. This causes a massive immune cell infiltration that further promotes inflammation, stimulates lipolysis, and fuels Insulin Resistance (IR), resulting in adipocyte dysfunction [31]. As a consequence, AT develops a local low-grade inflammatory microenvironment, which recruits inflammatory M1 macrophages, T cells, B cells, neutrophils, and mast cells. In contrast, the populations of M2 macrophages, T helper type 2 (Th2), and regulatory T cells (Treg) remain or even decrease in later stages of obese AT [29,32]. This changes the balance from a regulatory anti-inflammatory immune state with the secretion of immunoregulatory cytokines including interleukin-4 (IL-4), IL-5, IL-10, IL-13, and IL-33 to a highly inflammatory state causing the secretion of tumor necrosis factor-alfa (TNF-α), monocyte chemoattractant protein-1(MCP-1), IL-1β, interferon γ (IFN-γ), and IL-6, leading to the development of a systemic and chronic inflammation [32].

Inflammation and its associated inflammatory cytokines, including IL-6, TNF-α, IL-1β, and inflammatory factors like C-reactive protein (CRP), are all known to induce endothelial dysfunction in AT [33]. Moreover, the deregulated expression of adipokines like leptin and resistin in AT of obese patients causes increased expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), both leading to vascular dysfunction and oxidative stress. These factors contribute to dysfunctional/damaged endotelial cells and reduced angiogenesis worsening the hypoxic state of AT [34]. As a result, the extracellular microenvironment loses its flexibility, increases mechanical stress, restrains adipocyte expansion, and triggers adipocyte cell death and a sustained immune response in AT.

SARS-CoV-2 uses its viral spike (S) protein for the entry into target cells. The spike protein consists of two functionally distinct subunits. The surface subunit S1 recognizes and binds to the cellular receptor, whereas the transmembrane subunit S2 facilitates fusion of the viral membrane with the cell membrane [35,36]. Like SARS-CoV, SARS-CoV-2 spike protein binds to its receptor human ACE2 through its receptor-binding domain (RBD) mediating its entry into host cells [37,38]. ACE2 is a zinc metalloprotease, which shares homology with ACE in its catalytic domain [39]. It has 805 amino acids including an N-terminal signal sequence and a C-terminal membrane binding domain [40]. ACE2 contains a single HEXXH zinc-binding motif and inactivates the potent vasoconstrictive peptide angiotensin II (Ang II) by removing its C-terminal phenylalanine residue to yield heptapeptide Ang-(1$-$7). The most remarkable expression of ACE2 protein was found on lung alveolar epithelial cells, and enterocytes of the small intestine, while ACE2 is present in arterial and venous endothelial cells, and arterial smooth muscle cells in all organs including oral and nasal mucosa, nasopharynx, stomach, colon, liver, kidney and brain [41]. Moreover, based on bioinformatic and protein docking models, it has

been suggested that, like MERS-CoV, the spike RBD of SARS-CoV-2 binds to human dipeptidyl peptidase 4 (DPP4) with a high affinity in addition to ACE2 [42,43]. Furthermore, cluster of differentiation (CD147) is recently proposed to be an alternative receptor for SARS-CoV-2 binding on the cell surface [44], although it is structurally not yet validated.

SARS-CoV-2 spike protein is proteolytically activated at its S1/S2 cleavage site by human transmembrane protease serine 2 (TMPRSS2) [37]. Apart from TMPRSS2, SARS-CoV-2 spike protein can be proteolytically activated by a variety of other proteases including furin, elastase, factor X, and trypsin, indicating the interesting fact that coronaviruses favor as receptors various protease proteins. These proteases are capable to perform a "priming" proteolysis that initiates the process of cellular entry [45,46].

AT expresses various receptors and enzymes required for SARS-CoV-2 infection. ACE2, the functional receptor for SARS-CoV and SARS-CoV-2, is highly expressed in AT [47,48]. Its mRNA was detected in human AT, with higher ACE2 expression in visceral compared to subcutaneous AT. Most important, its expression is upregulated in adipocytes of patients with obesity and diabetes [49]. On this subject, studies show that every 10 cm^2 increase in visceral AT was associated with a 1.37-fold higher likelihood of Intensive Care Unit (ICU) treatment and 1.32-fold higher likelihood of mechanical ventilation in between hospitalized patients. And, for each additional centimeter of waist circumference, there were 1.13 increased risk for ICU treatment and 1.25-fold for mechanical ventilation [50,51].

Obesity results in ACE2 upregulation in AT of mice causing mild epicardial AT inflammation [52]. Recently, a study with COVID-19 patients showed that individuals with obesity demonstrate significantly higher levels of ACE2 in their blood serum [53].

Other suggested receptors for SARS-CoV-2 are also present in AT. DPP4, the potential SARS-CoV-2 receptor, is multifunctional including its roles in glucose homeostasis, inflammation, and the immune system [54]. Identified as a novel adipokine in AT, DPP4 is strongly expressed on the apical surfaces of the polarized epithelium of various organs such as lung and liver, and increased DPP4 results in failures to resolve inflammation and chronic subclinical activation of the immune system [54].

Interestingly, DPP4 is upregulated in obesity, especially in the IR state [55]. Inhibition of DPP4 prevented fibrosis in obese white AT [56]. AT, mainly specifically adipocytes, have been proposed to be a significant circulating source of DPP4 [57]. DPP4 secretion from AT was also demonstrated in vivo with greater release in individuals with obesity compared to lean individuals (Fig. 1). Thus, AT from patients with obesity highly expresses DPP4 and possibly is its major circulating source, which may facilitate the entry of SARS-CoV-2 into cells and also strong inflammation and violent immune response, important steps leading to the cytokine storm of COVID-19 [58].

In addition, given the low-grade chronic inflammatory response present in obesity, the immune response and chemotaxis are compromised with a subsequent disturbance in the immune surveillance system, causing not only greater susceptibility to airway diseases and further aggravation when installed [59], but also represents an important concern about the vaccination of these patients, considering the unsatisfactory vaccine response in individuals with obesity [59,60]. In this context, previous studies with different viral vaccines, including hepatitis A, hepatitis B, rabies, and most importantly, influenza, demonstrate lower vaccine response in patients with obesity [61,62]. And in relation to COVID-19, one study shows that patients with greater waist

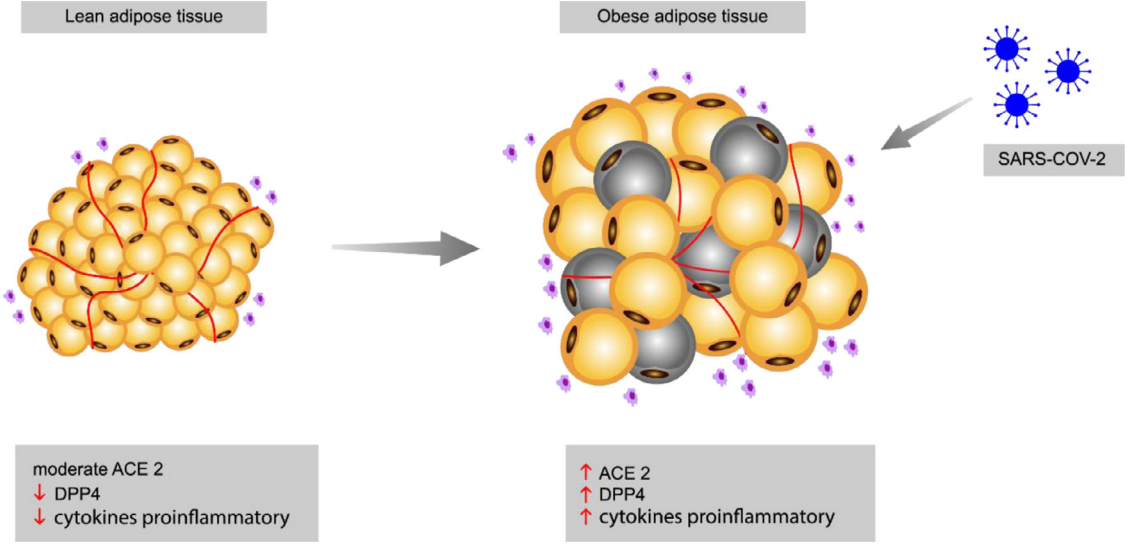

Fig. 1 Lean and obese adipose tissue under COVID-19. Legend: Characteristics of adipose tissue in lean state and obesity under COVID-19. Lean adipose tissue presents a moderate ACE2, lower production of DPP4 and cytokines pro-inflammatory. In obesity, there is a dysfunction of the adipose tissue with greater deposition of DPP4, ACE2 and pro-inflammatory cytokines, which contribute to high local infection of SARS-CoV-2, cytokine storm, and worse prognosis of COVID-19. DPP4: dipeptidyl peptidase 4; ACE2: Angiotensin-converting enzyme 2.

circumference had significantly lower antibody titers against SARS - CoV - 2 ($R = -0.324$, $p = 0.004$) compare with patients with smaller waist circumference, however, the same did not occur when evaluated in obesity only according to BMI $\geq$ 30 kg/m2 ($p = 0.524$) [63], which brings additional data about the discussion on the effectiveness of vaccination in individuals with obesity, especially visceral adiposity, and highlights of its effect in COVID-19, immune cell dysregulation and alterations in inflammatory signaling pathways.

MAFLD and SARS-cov-2

In the liver, ACE2 receptors are mainly expressed in cholangiocytes (60% of cells) and in endothelial cells, rather than in hepatocytes (3% of cells) or Kupffer cells (spot where ACE2 receptors are absent) [64]. Major factors involved in SARS-CoV-2 infection and liver damage are lung involvement leading to hypoxia, venous congestion with liver steatosis, role of immune cells and cytokines, drug-induced liver damage, addition of coagulation disorders and cytokine storm. MAFLD might represents, *per se*, a condition of intrinsic frailty, due to ongoing lipotoxicity, chronic inflammatory status, IR, oxidative stress and immune response, or be a marker of additional coexisting metabolic disorders which will aggravate the clinical course of COVID-19. A prior liver disease might exaggerate the damage from ongoing COVID-19 infection.

Liver damage in patients with COVID-19 can be due to various mechanisms, among which stand out the action of the virus or the immune system on the liver cells and toxicity of the drugs used in its treatment. Several mechanisms of damage could link COVID-19 to liver:

(i), a direct cytopathic viral damage once SARS-CoV-2 in gut lumen could translocate to the liver via portal flow and induce a direct damage due to active viral replication in hepatic cells through ACE2 receptors, and Kupffer cells trying to fight it would trigger local inflammation resulting in liver damage [65]. This effect is not necessarily linked to increased liver SARS-CoV-2 uptake, since MAFLD is not associated with changes in expression of liver genes implicated in SARS-CoV- 2 infection.

(ii), hepatocellular hypoxia in chronic liver diseases in COVID-19 patients might lead to increased expression of ACE2 receptors, and hypoxia-inducible factors (HIFs), a family of transcription factors activated by hypoxia. Such changes might further aggravate metabolic diseases such as MAFLD [66], aggravating MAFLD progression [67,68].

(iii) dysregulated systemic and hepatic innate immunity [69,70]. ACE2 receptors in enterocytes [71] would predispose to viral translocation to the liver with potentials for viral circulation via the reticular system [72]. The innate immune cellular cluster in the liver would be activated with inflammatory and changes due to cytokine production. Patients with severe COVID-19 infection display elevation of inflammatory biomarkers.

(iv), patients with pre-existing chronic liver disease may be more susceptible to liver damage from SARS-CoV-2. (v), lipid production and breakdown in the liver provide lipid species which negatively regulate the underlying status of chronic metabolic inflammation and complex network of factors acting within the liver can drive innate immune activation. This pathway directly triggers and amplifies hepatic inflammation [73].

Recent studies suggest that the virus may bind to ACE-2 receptors located on cells liver diseases, especially in cholangiocytes where their expression is more abundant [74,75]. In healthy livers are detect at low levels, while in cirrhotic liver ACE2 mRNA levels are up- regulated 34- fold and ACE2 protein 97- fold [76]. After its union with the receptor and entry into the cell, mechanisms of replication aimed at generating new viral RNA and synthesizing structural proteins necessary for the assembly and release of new viral particles [77]. As opposed, the expression of ACE-2 receptors in hepatocytes is scarce, which could explain the absence of analytical data and histological characteristics typical of viral hepatitis [78].

The renin-angiotensin system (RAS) can contribute to the pathophysiology of liver diseases, as a compensatory response to systemic and splanchnic arterial vasodilation [79]. In this context, Angiotensin II (Ang II) enhances intrahepatic resistance by promoting the proliferation and contraction of hepatic stellate cells and inducing the profibrogenic processes in the liver, related to harmful effects that influence the spectrum of histological changes observed in MAFLD [80].

In the RAS system, Ang II attaches to its receptor (Ang II type 1 receptor [AT1R]) while Ang (1−7) binds to MAS1 oncogene, leading to vasodilation and decreasing inflammation, cell proliferation, hypertrophy, and fibrosis [81]. Ang II can activate the NLRP3 inflammasome in hepatocyte and induce caspase-1-dependent cell apoptosis, promoting greater release of Interleucin (IL) -1β and IL-18 who act to endorse the process of liver inflammation, triglycerides deposition and IR, triggering MAFLD progression and greater liver damage [82].

In the COVID-19 infection, SARS-CoV-2 disrupts the ACE/ACE2 physiological balance and activates the Ang II/AT1R pathways, downregulation ACE2 and reduces the Ang (1−7) levels, which counter-regulates Ang II, and protect against hepatic fibrosis and oxidative stress [83], which could predispose patients with MAFLD a severe COVID- 19 clinical course and liver damage.

In some severe cases, hyperarousal has occurred pro-inflammatory immune system, the consequences of which could be more lethal than the viruses own cytopathic effect [84]. However, the consequences at the liver level of this dysfunction immune system in the context of COVID-19 are still unknown.

Other important point is drug-induced toxicity employed in the treatment of COVID-19 as well it can contribute to liver damage [85]. This is especially relevant, on the one hand, in patients with diseases pre-existing chronic liver diseases in which the risk toxicity is higher.

COVID-19 acute pandemic often develops in patients with major metabolic abnormalities, including fatty liver disease, which is part of a chronic pandemic together with body fat accumulation. During metabolic abnormalities, the expansion of metabolically active fat parallels chronic inflammatory changes [86,87], the development of IR, and in the liver, the accumulation of fat, possibly, an underlying fibrosis. About this, the deleterious interplay of the complex inflammatory pathways chronically present in MAFLD can be

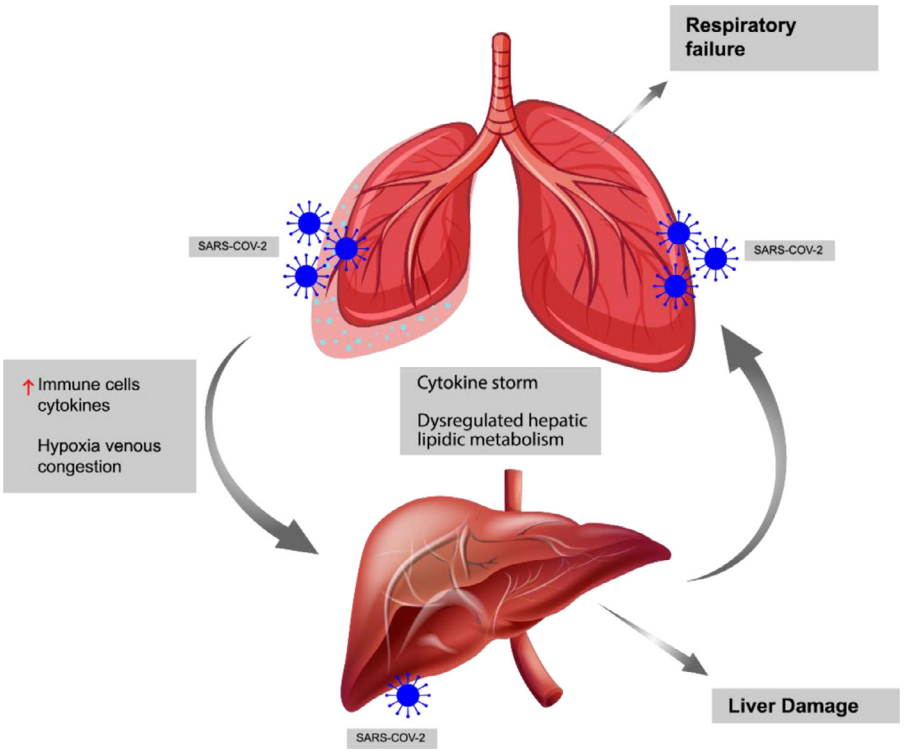

Fig. 2 Factors involved in COVID-19 associated with MAFLD. Legend: Metabolic pathways present in SARS-CoV-2 infection associated with liver damage. Patients with MAFLD have higher expression of ACE, ACE2 and Ang II, which favors the entry of the virus into the cell, and in the presence of the ACE2 downregulation by the virus, there is greater performance of Ang II, favoring dysregulated hepatic lipidic metabolism, increase of cytokines pro-inflammatory and cytokine storm, which predispose patients with MAFLD to severe COVID - 19 and liver damage.

acutely increased in the setting of COVID-19, magnifying liver injury and deteriorating outcome in metabolically compromised individuals (Fig. 2).

Finally, a further challenge in the diagnosis and treatment of MAFLD patients is to reduce the vulnerability from non-communicable diseases, increasing the individual resilience to future outbreaks.

Syndemia (Obesity, MAFLD and COVID-19)

Syndemia characterizes the mutually aggravating interaction between health problems in populations, and the present review demonstrates through recent findings that the prevalence of obesity, characterized by AT dysfunction and low-grade inflammation, associated with MAFLD in the current scenario of COVID-19 pandemic is, indeed, a real syndemia that needs to be treated and controlled, to provide more life expectancy worldwide.

Obesity affects the liver through adipokines, hormones derived from the AT, which may contribute to development of many stages of MAFLD (steatosis, non-alcoholic steatohepatitis [NASH], cirrhosis and carcinogenesis) [88,89]. Once, obese AT contains all components for SARS-CoV-2 infection could be targeted and even serve as a reservoir of viruses and an accelerator that reinforces brutal systemic inflammation and immune response, facilitating the development of a cytokine storm, a severe complication of COVID-19. Also, when obesity is not successfully managed at the stage of steatosis, an intrahepatic inflammatory process starts, possibly as an unsuccessful counterregulatory effort to limit this steatosis [90]. This process likens the low-grade inflammation occurring within the AT of individuals with obesity [91]. During this process, the hepatic innate immune cells, including Kupffer cells, dendritic cells and HSCs are activated, and the liver is progressively infiltrated by immune cells, including neutrophils, monocytes, T-lymphocytes and mainly macrophages [92]. Within the liver, the immune cells release cytokines that intensify the inflammatory process, but also contribute to fibrotic process, which is usually appeared when the inflammation prolongs [93]. During fibrogenesis, the immune cells crosstalk with wound-healing cells, including activated endothelial cells and myofibroblasts, within the liver. Following liver damage, the mentioned immune and wound healing cells are targeting to tissue regeneration [94]. Under normal circumstances, this counterregulatory mechanism succeeds in the replacement of hepatocytes subjected to cell death or apoptosis, but when this mechanism fails, mainly in continuous obesity and under severe acute respiratory syndrome as COVID-19, fibrosis occurs, possibly as an unsuccessful effort against liver injury and tissue regeneration [85].

Adipokines are unbalanced in obesity [90], during the enlargement of AT, the secreted adipokines shift towards a more steatogenic, inflammatory and fibrogenic profile. Immune cells (macrophages, B-lymphocytes, T-lymphocytes and neutrophils), infiltrating AT during its enlargement, also produce ILs and classical cytokines (i.e., IL-1, IL-6, TNF-α), which interplay with adipokines [88]. In addition, SARS-CoV-

2 may infect monocytes, macrophages, and dendritic cells resulting in their activation and secretion of IL-6 and other inflammatory cytokines [94]. The current epidemic of obesity and related metabolic diseases has extensively contributed to increase the number of severe cases and deaths from COVID-19. With serious results in a health, political and economic crisis with long-lasting consequences that will affect our ways of living and seeing public health policies about obesity, which have been discussed over the last decades, however, with low success rate [60].

In this sense, the impact between two pandemics, the recognition of obesity as a chronic disease and a great risk factor for COVID-19, may have been fundamental step towards advancing important debates about the implementation of public health policies to reduce and prevent the significant advance of obesity worldwide [95,96] (Fig. 3).

In summary, ACE2 is highly expressed in AT and adipocytes, and its expression is increased in obesity, which could turn AT into a potential target and viral reservoir. Obesity has been characterized by low grade chronic inflammation which leads to exacerbated and prolonged activation of both innate and adaptive immune responses, bringing on tissue damage and metabolic and physiologic alterations. Exacerbated inflammation is associated with increased risk of severe disease and mortality in patients with COVID-19. COVID-19 patients commonly present intense proinflammatory markers activation such as IL-1, IL-6, IL-17, IL-18, IFN, and CRP. According to studies developed until now, it is reasonable to assume that COVID-19-related liver dysfunction is more likely due to coexistence of systemic inflammatory response and respiratory distress syndrome-induced hypoxia.

Therefore, the presence of inflammatory pathways, mainly storm of cytokines, present either in obesity and in COVID-19 patients could increase liver inflammation or be a marker of metabolic risk factors further aggravating the clinical outcome. Thus, MAFLD should be considered as prognostic indicator during COVID-19.

This review not only emphasizes the impact of the presence of MAFLD during the COVID-19 pandemic, as well as the associated metabolic pathways, but also discusses the interrelationship of obesity, MAFLD and COVID-19, that converged in a worrisome metabolic scenario and impacted significantly to public health. A syndemia that needs to be considered so that the adoption of treatment and control measures can provide longer life expectancy, mainly with good quality, worldwide.

Considering that the mortality and morbidity observed in COVID-19 patients is associated with excessive inflammation and the presence of liver damage, a better understanding of the immunological parameters seen in patients infected with SARS-CoV-2 is necessary to better correlate obesity, MAFLD and COVID-19, improving the identification of therapeutic targets.

Core tip

Recently, obesity has been considered an important and independent predictor for coronavirus disease 2019 (COVID-19) complications in adults. In state of obesity have been observed changes in the composition, structure, and function of adipose tissue (AT). The liver can also become a

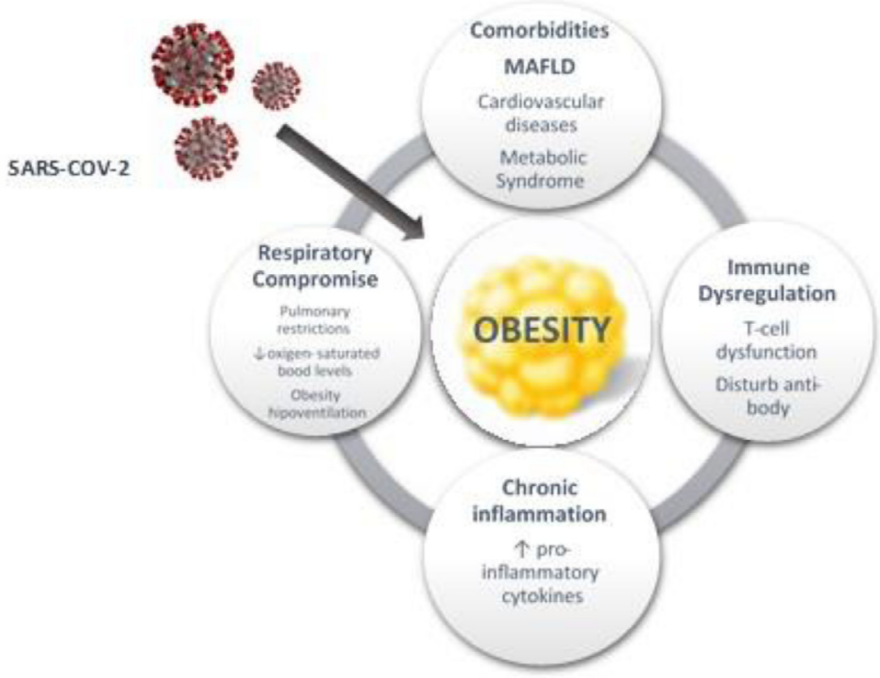

Fig. 3 Interactions of outcomes from obesity, MAFLD and COVID-19. Legend: Obesity is an independent risk factor for the installation and progression of MAFLD, and when they are associated present metabolic characteristics that favor the setup and worsening of COVID-19, which in turn, potentiate inflammation and immune dysregulation, already present in these individuals, resulting in liver damage and worse prognosis.

target of COVID-19 infection. SARS-Cov-2 might affect the liver by direct or indirect mechanisms.

The present review demonstrates that the prevalence of obesity, characterized by AT dysfunction and low-grade inflammation, associated with MAFLD in the current scenario of COVID-19 pandemic is, indeed, a real syndemia that needs to be treated and controlled, to provide more life expectancy worldwide.

Author contributions

CA participated in the conceptualization, writing original draft of the manuscript, writing - review & editing and visualization. RAm participated in writing - review & editing and RA participated in supervision, validation and writing - review & editing. All authors read and approved the final manuscript.

Disclosure

The authors declared no conflict of interests.

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